Remarks

Claims 2, 6, 11, 12, 15-21, and 23-31 are pending in this application. Applicants note with appreciation that the Examiner has indicated that claims 6 and 23-31 are allowed. In light of the following remarks, applicants respectfully request reconsideration of this application and allowance of all of the pending claims to issue.

Interview Summary

Applicants wish to thank Examiner Tung for granting the request for and participating in the telephonic interview held on August 19, 2011 with Applicants' representative, Dr. Alice Bonnen. During this interview the obviousness rejection raised in the present Office Action was discussed.

Rejections under 35 U.S.C. §103(a)

A. Claims 2, 11-12, and 16-18 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Laue (U.S. Patent No. 7,374,883) in view of Lowe et al. (Nucleic Acids Res. 18:1757-1761 (1990)).

The Office Action alleges that the response filed on April 26, 2011 (hereinafter "the April 26, 2011 response") does not provide evidence that these primer pairs for amplifying SARS CoV RNA work better than others.

As presented herein, claim 2 recites a pair of oligonucleotides for amplification of a target sequence of the genome of SARS coronavirus, said pair selected from the group consisting of: (a) a first oligonucleotide sequence of SEQ ID NO:4: TAGTAGCTGT ACCGACTGGT TATGTT, or the complementary nucleotide sequence of SEQ ID NO:4, and a second oligonucleotide sequence of: SEQ ID NO:7: GAAGCTATTC GTCACGTTCG, or the complementary nucleotide sequence of SEQ ID NO:7; (b) a first oligonucleotide sequence of SEQ ID NO:3: TCCACCAGGT GACCAGTTTA AACATCTT, or the complementary nucleotide sequence of SEQ ID NO:3, and a second oligonucleotide sequence of SEQ ID NO:8: TGCGTGGATT GGCTTTGATG T, or the complementary nucleotide sequence of SEQ ID NO:8; (c) a first oligonucleotide sequence of SEQ ID NO:25: TTGGCATGGA AGTCACACCT T, or the complementary nucleotide sequence of SEQ ID NO:25, and a second oligonucleotide sequence of SEQ ID NO:29: CAGAACAAAC CCAAGGAAAT T, or the complementary nucleotide sequence of SEQ ID NO:29; and any combination of (a) through

(c) above. Thus, claim 2 recites the primer pairs as suggested in the Office Action dated December 27, 2010, wherein it was stated "[r]egarding the arguments filed 11/04/10, the response points to examples from the specification showing these primer pairs for amplifying SARS CoV RNA exhibited better performances than others. However, this argument and the examples in the specification are not commensurate in scope with the instant claims, which are much broader and encompass a large number of primer pairs. There is no evidence of record that all of the primer pairs encompassed in the genus recited in the claims would be expected to exhibit the same advantageous properties as the specific primers which were tested. Claims limited to the tested primers would not be subject to this rejection." (Office Action dated December 27, 2010, paragraph bridging pages 6 and 7, emphasis added). Since claim 2 recites the tested primers, applicants respectfully submit that the claim 2 should not be subject to the present rejection. Accordingly, applicants submit that claim 2 and claims dependent thereon are patentable over Laue in view of Lowe et al.

However, the present Office Action alleges that the April 26, 2011 response does not provide evidence that these primer pairs for amplifying SARS CoV RNA work better than others. In the interview with Examiner Tung, applicants pointed to the response submitted on November 4, 2010 (hereinafter "the November 4, 2011 response"), which provides such evidence. However, applicants were then requested to provide additional discussion comparing the claimed SARS primers with other SARS primers that do not work as well. Accordingly, applicants present the requested discussion below.

The genome of the SARS coronavirus is approximately 29,750 bases in length. Laue discloses a 300 nucleotide sequence of the SARS genome and from this sequence provides particular primer pairs for detection of SARS using PCR. However, Laue fails to teach or suggest the specific primer pairs of the presently claimed invention. Further, the secondary reference, Lowe et al., fails to remedy the deficiencies of Laue.

Lowe et al. provides a program for finding, in a selected sequence, those sequences that fulfill the criteria designated by the user for the desired primers. The Office Action asserts that Lowe et al. would allow for selection of primers for PCR from a known sequence. However, the Lowe et al. program is not sufficient for identifying useful SARS coronavirus primers as defined by the claimed invention, for at least the reason that after selecting the target sequence, the ordinary skilled person using the program must still single out and select the presently claimed pairs of primers from the large

number of possible primers produced by the program. As noted above, the SARS coronavirus genome is over 29,750 bases in length; thus, the potential number of different primers and primer pair combinations would be exceedingly large. Even inputting the 300 bases of the nucleotide sequence of Laue would result in an extremely large population of primers, with no direction provided for how to select among the primers or how to select for specific primer pairs. Nothing in the cited art teaches or suggests or provides any direction for selecting the specific primer pairs of the present invention.

Further, data in the present specification show that the claimed pairs of oligonucleotides have greater sensitivity and/or better kinetics when compared to other primer pair combinations developed from SARS. For example, Figs. 1-5 and 7-11, Tables 1 and 3, and pages 25-26 and 33-34 show and discuss the superior kinetics and the lower time to positivity for SARS-COV-Rep primer pair P1.1/P2.2 (SEQ ID NO:10 (SEQ ID NO:4)/SEQ ID NO:7) and P1.3/P2.3 (SEQ ID NO:9 (SEQ ID NO:3)/SEQ ID NO:8) as compared to other primer pairs for SARS-COV Rep. Further, the increased sensitivity of the SARS-COV-N (region 2) primer pair P1.4/P2.6 (SEQ ID NO:42 (SEQ ID NO:25)/SEQ ID NO:29) is shown in Figs. 35-40 and discussed in the paragraph bridging pages 47-48.

To distinguish primer pairs, each primer pair was tested for its ability to amplify different dilutions of SARS RNA as compared to other primer pairs tested at the same dilutions of SARS RNA. Specifically, Figures 1-4 show the amplification curves of four different primer pairs including primer pair P1.1/P2.2, which corresponds to claimed primer pair SEQ ID NO:10 (which is SEQ ID NO:4 plus the T7 polymerase promoter sequence) and SEQ ID NO:7. The results show that when analyzed for the time at which the different reactions reveal fluorescence signals that are well above background, the claimed primer pair, P1.1/P2.2 showed a strikingly lower time-to-positivity value (i.e., faster kinetics) as compared to primer pairs P1.1/P2.1, P1.2/P2.2, and P1.2/P2.1 (*See,* Figure 3 (P1.1/P2.2) as compared to Figure 1 (P1.1/P2.1; correlate to SEQ ID NOs:10 and 6), Figure 2 (P1.2/P2.2; correlate to SEQ ID NOs:11 and 7) and Figure 4 (P1.2/P2.1; correlate to SEQ ID NOs: 11 and 6)).

Further, primer pair P1.3/P2.3, which correlate to claimed primer pair SEQ ID NO:9 (which is SEQ ID NO:3 plus the T7 polymerase promoter sequence) and SEQ ID NO:8, also showed a lower time-to-positivity value and faster kinetics when compared to primer pairs P1.2/P2.3, P1.3/P2.1 and P1.3/P2.2 (*See,* Figure 11 (P1.3/P2.3) as compared to Figure 8 (P1.2/P2.3; correlate to SEQ ID NOs:11 and 8), Figure 9 (P1.3/P2.1; correlate to SEQ ID NOs: 9 and 6) and Figure 10 (P1.3/P2.2; correlate to

SEQ ID NOs:9 and 7). Primer pair P1.1/P2.3 showed comparable kinetics to those of claimed primer pair P1.1/P2.2 (*See*, Figure 7 (P1.1/P2.3; correlate to SEQ ID NOs:10 and 8)).

Finally, for primer pairs that amplify SARS-COV-N (region 2), primer pair P1.4/P2.6 (SEQ ID NO:42 (SEQ ID NO:25 plus the T7 polymerase promoter sequence)/SEQ ID NO:29) is compared to that of primer pairs P1.3/P2.3, P1.3/P2.4, P1.3/P2.6, P1.4/P2.3 and P1.4/P2.4. Thus, in Figure 40, primer pair P1.4/P2.6 shows increased sensitivity as compared to the other primer pairs in that at least, for example, only the P1.4/P2.6 primer pair was able to amplify the virus at the lowest dilution of 10^9 (*See,* Figure 40 (P1.4/P2.6) as compared to Figure 35 (P1.3/P2.3; correlate to SEQ ID NOs:41 and 27), Figure 36 (P1.3/P2.4; correlate to SEQ ID NO:41 and 28), Figure 37 (P1.3/P2.6; correlate to SEQ ID NOs:41 and 29), Figure 38 (P1.4/P2.3; correlate to SEQ ID NOs:42 and 27), and Figure 39 (P1.4/P2.4; correlate to SEQ ID NOs:42 and 28).

Thus, it is clear that not all primers and primer pairs prepared for amplification and detection of SARS are functionally equivalent to the claimed primer pairs. These results are surprising and could not have been predicted nor could any computer program such as that of Lowe et al. have selected these particular primer pairs out of the 29,750 bp nucleotide sequence of the SARS genome or even the 300 bp nucleotide sequence of Laue.

Thus, the cited references fail to teach or suggest the specific primers of the presently claimed invention, they fail to provide the motivation to combine the cited references in order to achieve the presently claimed invention and even if combined the cited references fail to provide a reasonable expectation of success in achieving the presently claimed invention.

Accordingly, applicants submit that the pending claims are patentable over Laue in view of Lowe et al., and respectfully request the withdrawal of this rejection.

B. Claims 2 and 20 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Briese et al. (U.S. Patent Publication No 20040265796) in view of Lowe et al.

As discussed above, claim 2 recites the primer pairs suggested by the Examiner in the Office Action dated December 27, 2010 (page 7). For at least the same reasons discussed above for claim 2 being patentable over Laue in view of Lowe et al., the recited primer pairs are also patentable over Briese et al. in view of Lowe et al. Accordingly, applicants respectfully request the withdrawal of this rejection.

C. Claim 15 stands rejected under 35 U.S.C. §103 as allegedly being unpatentable over Laue in view of Lowe et al. in further view of Tyagi (*Nature Biotechnol.* 14:303-308 (1996)).

Claim 15 depends from claim 2. Thus, for at least the same reasons set forth above regarding claim 2, applicants submit that claim 15 is patentable over Laue in view of Lowe et al. in further view of Tyagi and therefore respectfully request the withdrawal of this rejection.

D. Claims 19 and 21 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Laue in view of Lowe et al. in further view of Compton (*Nature* 350:91-92 (1991)).

Claims 19 and 21 depend from claim 2. For at least the same reasons discussed above for claim 2, applicants submit that claims 19 and 21 are patentable over Laue in view of Lowe et al. in further view of Compton and therefore respectfully request the withdrawal of this rejection.

The points and concerns raised in the Action have been addressed in full herein. Therefore, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested. Should there be any remaining concerns, the Examiner is encouraged to contact the undersigned attorney by telephone to expedite the prosecution of this application.

No fee is believed due. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

Alice M. Bonnen
Registration No.: 57,154

Customer Number 20792
Myers Bigel Sibley & Sajovec, P.A.
P.O. Box 37428
Raleigh, North Carolina 27627
Telephone: (919) 854-1400
Facsimile: (919) 854-1401

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Claire Wimberly